PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: BRET E. FIELD
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MENLO PARK, CALIFORNIA 94025

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	09 NOV 2000

Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**	
CLON-008W0		
International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/24070	13 OCTOBER 1999	13 OCTOBER 1998
Applicant		
CLONTECH LABORATORIES, INC.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DOCKETED 11/21

New citation
Suppl IDS due US
by 1/16/2001 (Friday)

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ARUN CHAKRABARTI (703) 306-5818

Form PCT/IPEA/416 (July 1998)*

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CLON-008W0	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/24070	International filing date *(day/month/year)* 13 OCTOBER 1999	Priority date *(day/month/year)* 13 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6; 536/25.3		
Applicant CLONTECH LABORATORIES, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [✓] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand 29 MARCH 2000	Date of completion of this report 13 OCTOBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ARUN CHAKRABARTI Telephone No. (703) 305-5818

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/24070

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain*

☐ the international application as originally filed.

☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____.
pages _____ , filed with the letter of _____.

☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/~~fig~~ (See Attached) , as originally filed.
sheets/~~fig~~ _____ , filed with the demand.
sheets/~~fig~~ _____ , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.

☒ the claims, Nos. NONE.

☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/24070

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-56	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-56	NO
Industrial Applicability (IA)	Claims	1-56	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-56 lack an inventive step under PCT Article 33(3) as being obvious over Nguyen et al. (Genomics, (1996), Vol. 29, pages 207-216.in view of Pinkel et al. (U.S. Patent 5,690,894) 25 November 1997.

Nguyen et al teach an array comprising at least one pattern of probe oligonucleotide spots stably associated with the surface of a solid support, wherein each probe oligonucleotide spot corresponds to a target nucleic acid and comprises an oligonucleotide probe composition made up of a plurality of unique oligonucleotides (Abstract and Figures 1-8).
Nguyen et al teach an array wherein the plurality of unique oligonucleotides are capable of hybridizing to different regions of the corresponding nucleic acid of the oligonucleotide spot in which they are positioned (Figure 1 and MATERIALS AND METHODS Section, page 208, second and third paragraph).
Nguyen et al teach an array wherein the plurality of unique oligonucleotides hybridize to non-overlapping regions of the target nucleic acids and two or more different target nucleic acids are represented in the pattern(RESULTS Section, Page 212, column 2, second paragraph).

Nguyen et al teach an array wherein the plurality of unique oligonucleotides hybridize to overlapping regions of the target nucleic acids (Figure 4).
Nguyen et al teach an array wherein each probe oligonucleotide spot in the pattern corresponds to the same or different target nucleic acid (Figures 5 and 7,and Page 212, column 2, second paragraph).
Nguyen et al teach an array comprising a plurality of the patterns which are separated from each other by walls(MATERIALS AND METHODS Section, Page, 208, first paragraph and Figures 1-8).

Nguyen et al teach an array wherein the legth of each oligonucleotide ranges from about 15 to 150 nucleotides (Resilts Section, Page 212, column 1, firs paragraph).
Nguyen et al teach an array wherein the array comprises at least one mismatch probe (Figures 1, 2 and 4).
(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
pages, 1-23, as originally filed,
pages, none, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
numbers, NONE, as originally filed.
numbers, NONE, as amended under Article 19.
numbers, NONE, filed with the demand.
and additional amendments:
Pages 24-29 filed with the letter of 26 September 2000.

This report has been drawn on the basis of the drawings,
sheets, NONE, as originally filed.
sheets, NONE, filed with the demand.
and additional amendments:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
Nguyen et al teach an array wherein the number of oligonucleotides of each of the oligonucleotide probe composition ranges from about 3 to 50 (Page 212, column 2, second paragraph).
Nguyen et al teach an array wherein the number of spots on the array ranges from abiut 50 to 10,000 (MATERIALS AND METHODS Section ,page 208, column 2, third paragraph).
Nguyen et al teach an array wherein the density of spots on the array does not exceed about 1000/cm square (MATERIALS AND METHODS Section ,page 208, column 2, third paragraph).

Nguyen et al teach an array comprising at least one pattern of probe oligonucleotide spots stably associated with the surface of a solid support, wherein each probe oligonucleotide spot corresponds to a target nucleic acid and comprises an oligonucleotide probe composition made up of 3 to 50 unique oligonucleotides of from about 15 to 150 nucleotides in length, wherein each oligonucleotides is capable of hybridizing to different regions of the corresponding nucleic acid of the oligonucleotide spot in which they are positioned (MATERIALS AND METHODS Section, page 208, column 2, second and third paragraph).

Nguyen et al teach a method of preparing an array comprising at least one pattern of probe oligonucleotide spots stably associated with the surface of a solid support, wherein each probe oligonucleotide spot corresponds to a target nucleic acid and comprises an oligonucleotide probe composition made up of a plurality of unique oligonucleotides, the method comprising:
generating the unique oligonucleotides (MATERIALS AND METHODS Section ,page 208, column 1, second paragraph to column 2, third paragraph); and
stably associating the unique oligonucleotides on the surface of the solid support in a manner sufficient to produce the array (MATERIALS AND METHODS Section ,page 208, column 1, second paragraph to column 2, third paragraph).
Nguyen et al teach a method wherein the solid support is flexible, rigid, nylon or glass ((MATERIALS AND METHODS Section ,page 208, Library and high-density filter Subsection).

Nguyen et al teach a hybridization assay comprising the steps of:
contacting at least one labeled target nucleic acid sample with an array under conditions sufficient to produce a hybridization pattern (MATERIALS AND METHODS Section ,page 208, Column 2, Second paragraph); and
detecting the hybridization pattern (MATERIALS AND METHODS Section ,page 208, Measurement of hybridization signal Subsection).
Nguyen et al teach a hybridization assay wherein the method further comprises washing the array prior to the detecting step (Materials and Methods Section, Page 208, column 2, third paragraph).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Nguyen et al teach a method further comprising preparing the labeled target nucleic acid (Materials and Methods Section, Page 208, column 2, first and second paragraph).
Nguyen et al teach a method where the method further comprises:
generating a second hybridization pattern (Figure 5); and
comparing the hybridization procedure (Figure 5).
Nguyen et al teach a method where the hybridization patterns are generated on the same or different array (Figures 5 and 8).

Nguyen et al. do not teach an array wherein each oligonucleotide probe composition of each probe spot contains two or more different probes of different sequence that hybridize to the same target nucleic acid.
Pinkel et al. teach an array wherein each oligonucleotide probe composition of each probe spot contains two or more different probes of different sequence that hybridize to the same target nucleic acid.(Column 15, line 56 to column 16, line 3 and column 19, lines 56-67).
It would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine two or more different probes of different sequence that hybridize to the same target nucleic acid of Pinkel et al. in the array of Nguyen et al., since Pinkel et al. states,"It is an advantage of the disclosed apparatus and process that the constructed array can be tailored to rapid screening of extensive arrays of biological binding partners. Using already identified information, arrays can be assembled which can simultaneously and rapidly survey samples nucleic acid variations across entire genomes (Column 5, lines 20-25)". An ordinary practitioner would have been motivated to combine and compare two or more different probes of different sequence that hybridize to the same target nucleic acid of Pinkel et al. in the array of Nguyen et al. in order to achieve the express advantage, as noted by Pinkel et al, of a method which provides arrays that can be tailored to rapid screening of extensive arrays of biological binding partners and which can simultaneously and rapidly survey samples nucleic acid variations across entire genomes.

Applicant's amendment and argument with regard to claim numbers 1, 18, 31, 38 and 44 (filed on September 26, 2000), have been fully considered but are moot in view of the new ground of objection.

---------- NEW CITATIONS ----------
US 5,690,894 A (PINKEL et al) 25 NOVEMBER 1997, see entire document.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: BRET E. FIELD
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing *(day/month/year)* 02 FEB 2000	
Applicant's or agent's file reference CLON-008W0	**FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US99/24070	International filing date *(day/month/year)* 13 OCTOBER 1999
Applicant CLONTECH LABORATORIES, INC.	

RJB
RSB
BEF

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

DOCKETED 4/2/00
ART 19 4/2/2000
IAS IN US 5/2/2000

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ARUN CHAKRABARTI
Facsimile No. (703) 305-3230	Telephone No. (703) 306-5818

Form PCT/ISA/220 (January 1994)★ *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CLON-008W0	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/24070	International filing date *(day/month/year)* 13 OCTOBER 1999	(Earliest) Priority Date *(day/month/year)* 13 OCTOBER 1998
Applicant CLONTECH LABORATORIES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.